

Magnetic Resonance Spectroscopy in Clinical Practice

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I. Introduction

The first mention of magnetic properties is in Ancient Greek texts dated circa 1000 BCE. The shepherd Magnes noticed that his shoes and the tip of staff stuck fast in a magnetic field while he tended his flocks. He called the material, which subsequently became known as a magnetic oxide of iron (Fe_3O_4), magnetite^[1]. This phenomena was well known enough by 600 BCE that the first of the ancient Greek philosophers known to us, Thales, argued this magnetic stone proved that a life force suffused all matter^[2]. The modern scientific principles of nuclear magnetic resonance were first described in 1946 by Purcell et al and Bloch et al who received the Nobel Prize in 1952^[3, 4].

Using these principles and manipulations based on them, nuclear magnetic resonance spectroscopy (NMRS) employs standard or research-dedicated magnetic resonance imaging (MRI) scanners to non-invasively assess the metabolism and chemistry of the human brain.

When compared with other *in vivo* neurochemical measurement techniques, such as PET and SPECT, an important advantage of MRS is that patients are not exposed to ionizing radiation and studies can be performed an unlimited number of times and at any interval required by the clinical or experimental situation. The ability to perform MRS in the same setting with MRI, without the injection of radioactive isotopes or blood sampling, provides important relative advantages for MRS over PET.

At the same time, MRS has lagged behind the development of structural MRI for several reasons, including technical requirements for data acquisition/analysis.

Recent technological advances and the increasing availability of scanners with 3 or 4 Tesla magnetic fields, however, have improved the sensitivity of MRS scans, and while long acquisition times have previously been a barrier to some research endeavors, MRS scan times can now be reduced to 3- to 15-minutes.

MRS provides an opportunity to gain *in vivo* information including neuronal viability or function, bioenergetics, cell membrane turnover, levels of several medications and activity of neurotransmitters^[5, 6]. Indeed, MRS can be, has been, and will be used clinically with a focus on improving diagnosis and

treatment by virtue of an enhanced understanding of neurochemical changes associated with a number of pathologic processes.

In this syllabus, the principles of MRS and the current status of MRS studies in psychiatry will be reviewed with emphasis on clinical usage.

II. Principles of MRS

A few orienting comments regarding basic physical principles will aid this discussion. First, atomic nuclei act like tiny magnetic dipoles making their own magnetic field with precession (spinning). Net magnetization resulting from the magnetic fields of atomic nuclei contributes to the phenomenon of magnetic resonance (Figure 1).

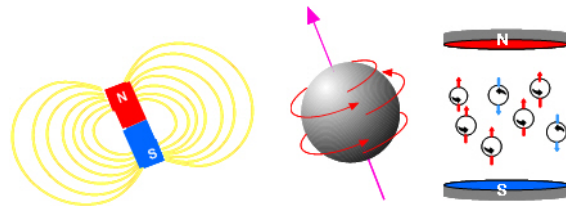


Figure 1. Magnetic dipole, Atomic nuclei, and magnetism in a uniform magnetic field

MRS takes advantage of subtle differences in the magnetic environment of nuclei within specific molecules, resulting in slight chemical shifts (expressed as parts per million from the main frequency) that depend on the electron fields of neighboring nuclei. Methods that allow localization of the acquired spectra from a single brain volume and from multiple voxels (three dimensional units within regions of interest), termed chemical shift imaging (CSI), have been developed.

1. Proton MRS

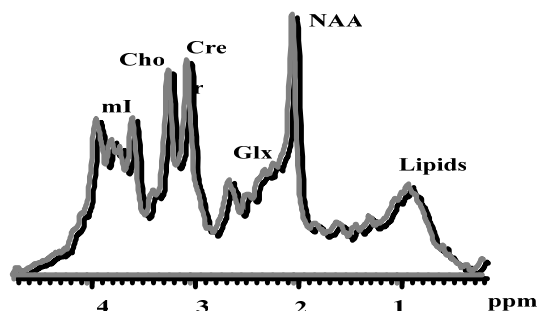


Figure 2. Illustration of a Proton MR Spectrum

Proton (^1H) MRS involves the acquisition of spectra with multiple discernable peaks, as illustrated above. From these spectra, it is possible to identify alterations in cerebral concentrations of N-acetyl aspartate (NAA), phosphocreatine (PCr), creatine (Cr), choline containing compounds (Cho), glutamate/glutamine (Glx), myo-inositol (mI), and lactate (Figure 2). An abbreviated list of relevance in practice follows.

- NAA: used as a neuronal marker
- Cho: (phosphocholine/glycerophosphocholine); membrane turn-over & myelination
- Cr (creatine + phosphocreatine): historically used as an internal reference
- mI: primarily an osmolyte, possible glial marker
- Lactate: increases with impairments in oxidative metabolism
- Glx (glutamate/glutamine/GABA): separable using modeling
- GABA: requires special detection/analysis methods

Various data acquisition techniques have been developed, with special adaptations to physical and clinical exigencies.

2. Phosphorus-13 MRS

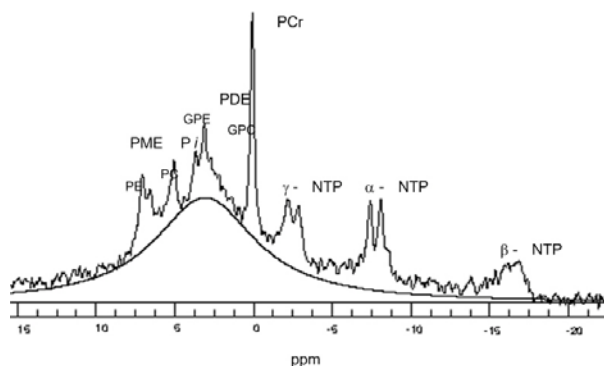


Figure 3. A Phosphorus MR Spectrum

Phosphorus-31 (^{31}P) MRS provides methods of studying changes in high-energy phosphate metabolites such as phosphocreatine (PCr) and adenosine triphosphate (ATP). Molecules involved in phospholipid metabolism, including the phosphomonoesters (PME), phosphodiester (PDE), and inorganic phosphate, can also be detected (Figure 3. above)

3. Fluorine-19 (^{19}F) MRS

^{19}F is 100% naturally abundant and has an MRS sensitivity of 83% relative to protons [7]. The brain tends to accumulate these agents at levels which are an order of magnitude higher than serum levels due to (1) their lipophilicity (affinity with fat cells) and (2) pH trapping in acidic vesicles [8] consequently making drug resonances MRS-visible [9]. ^{19}F MRS has been effectively used in understanding pharmacokinetics in target organs and correlating brain concentrations of SSRIs like fluvoxamine, fluoxetine, and paroxetine with clinical responses [10-12].

III. Current Status of MRS in Studies of Psychiatric Disorders

1. Schizophrenia

1) General findings

Two major findings have emerged in MRS studies of schizophrenia. The first is decreased PME and increased PDE in the frontal lobe by ^{31}P -MRS [13-15]. The second is focal decreases in NAA in the thalamus, frontal and temporal lobes [13, 16-20].

These phosphorous findings have been related to the neurodevelopmental process of "pruning," in which many synapses are eliminated during late childhood and adolescence [21-23]. Decreased NAA suggests decreased neuronal density or neuronal dysfunction of the specific regions. Jakary et al have interpreted decreased NAA as a mitochondrial metabolic deficit due to disease pathology or medication effect [20].

Deicken et al reported that β -NTP levels within the basal ganglia were decreased (by 11%) in subjects with chronic schizophrenia [24]. They also documented schizophrenic subjects evincing decreased NAA levels in the anterior cerebellar vermis compared to healthy comparison subjects [25]. In addition, there is a recent report that cerebellar cortex and vermis have decreased NAA levels in schizophrenia. The cerebellum has been regarded as one of the important brain regions of pathophysiology of schizophrenia [26].

Kegeles et al assessed the hippocampus in schizophrenic subjects using both MRI and MRS [27]. They reported a lateralized abnormality of GABA, but no significant hippocampal volume deficit or asymmetry. Returning to NAA, Ende et al reported that age-corrected NAA signal decreases in the anterior cingulate region correlate with duration of illness [28].

Recently, Tebartz van Elst and colleagues reported increased glutamate levels in prefrontal and hippocampal areas of schizophrenic patients compared to a healthy comparison group [29]. This may reflect glutamatergic abnormality in schizophrenia.

2) Neuroleptic-naïve schizophrenia patients

MRS studies of medication-naïve patients provide one method of dissociating pathophysiology and medication effects. In neuroleptic-naïve schizophrenia subjects, Gangadhar et al found decreased phosphocreatine (PCr) in the basal ganglia as measured with ³¹P MRS [30].

Further supporting the general finding mentioned above, decreased NAA levels have been observed in the frontal and temporal lobes [31] and hippocampus [32] of neuroleptic-naïve patients with schizophrenia as compared to healthy comparison subjects, [31-36].

In addition, a study using 4.0 Tesla ¹H-MRS has shown increased Glx levels, but not in NAA levels, in the anterior cingulate and thalamus of neuroleptic-naïve patients [34]. Likewise there is a report of increased Cho levels, but not NAA levels, in the caudate of neuroleptic-naïve patients [36].

An elevated PME/PDE ratio in the basal ganglia, as measured by ³¹P-MRS, has also been reported in neuroleptic-naïve patients [35]. In this study, the PME/PDE ratio notably correlated with symptom severity.

3) Antipsychotic effects

MRS has been increasingly used for evaluating neurochemical changes following typical and atypical antipsychotic medications [37-40].

A decrease in PDE levels in the temporal lobe [41] and an increase in frontal lobe [42] has been observed following 12 weeks and 3 weeks of neuroleptic treatment, respectively.

Bustillo et al have reported in a longitudinal follow-up ¹H-MRS study that frontal NAA concentration was reduced after 1 year of antipsychotic treatment [43].

Goff et al conducted a proton MRS study in subjects with schizophrenia, whose medication changed from haloperidol to olanzapine. Subjects with improvement in negative symptom showed an increase in glutamate concentrations compared to non-

responders [39]. Braus et al have reported that schizophrenic patients who were taking atypical antipsychotics showed greater NAA levels in the anterior cingulate compared to those who were taking typical antipsychotics [37, 38]. Theberge et colleagues conducted a ¹H MRS study in chronically medicated schizophrenia, and found decreased Glx levels in the left anterior cingulate, which could be the effect of neurodegeneration or chronic medication [44]. More recently, metabolic changes during risperidone treatment were reported: increased ml and NAA were observed in the thalamus [45].

4) Schizophreniform disorder and schizotypal personality disorder

As in schizophrenia findings, NAA ratios in the dorsolateral prefrontal cortex and hippocampus were lower in subjects with schizophreniform disorder compared to healthy comparison subjects [46]. Further, NAA ratios in these subjects correlated negatively with working memory. In addition, smaller PME level in the temporal lobe was reported in subjects with schizotypal personality disorder [47].

2. Major Depressive Disorder (MDD)

1a) General findings: ¹⁹F MRS

Because most of the serotonin-specific reuptake inhibitors (SSRI) employed in the treatment of depression are fluorinated compounds, ¹⁹F MRS has been utilized to understand pharmacokinetics in target organs and correlate brain concentrations of SSRIs with clinical responses [10-12]. By applying magnetization transfer methods to acquire ¹⁹F-MRS data, Strauss and Dager measured the relative contribution of unbound, versus bound, fluoxetine and metabolites to the "MRS-visible" signal *in vivo* [48]. Signals from the bound form of fluoxetine/norfluoxetine were approximately 14.2% of those detected from the unbound form.

¹⁹F MRS can also be useful in exploring *in vivo* SSRI-trapping in human body. Bolo et al performed ¹⁹F MRS in lower extremities and found "sequestration" of fluvoxamine and fluoxetine at bone marrow in subjects whose signal from plasma and brain had disappeared months before [49].

For drug development purposes, the therapeutic brain concentrations of different SSRIs can be measured by ¹⁹F MRS. Most recently, Henry et al compared brain drug levels achieved by two compounds, R-fluoxetine and racemic fluoxetine, using ¹⁹F MRS [50]. They demonstrated that more than 120 mg/day of R-fluoxetine would be required to acquire

the same levels of active drug as those of 20 mg/day of racemic fluoxetine in healthy subjects.

1b) General findings: ^1H and ^{31}P MRS

Proton MRS studies have documented both increases^[51-54] and decreases^[55-57] in the intensity of the ^1H -MRS Cho resonance in depressed populations. Variation in reported results may reflect differences in the brain regions studied, the acquisition parameters employed, or the characteristics of the study subjects. Nonetheless, baseline estimates of Cho signal intensity, as well as change with treatment, have been shown to correlate with clinical response^[55, 58]. Changes in the Cho resonance may reflect alterations in intraneuronal signal transduction^[59], in local glucose metabolism^[60], or in endocrine status^[61]. However, taken together, these studies raise the possibility that choline may play an important role in pathophysiology of depression.

Depressed subjects have been reported to show decreased *myo*-inositol levels in the frontal and anterior cortex relative to age- and sex-matched healthy comparison subjects^{[62] [63]}. This implies the possibility that the phosphatidylinositol second messenger system may be reduced in depression.

Sanacora et al have reported that occipital lobe GABA levels are dramatically reduced, by greater than 50%, in persons with major depression^[64]. This finding is in line with the GABA hypothesis for mood disorders, which suggests that low GABA function is an trait marker of vulnerability for their development^[65].

In partial contrast, most recently, Hasler et al have found, using a homogeneous resonator coil, that prefrontal lobe GABA levels are not significantly different in remitted depressed subjects from those of healthy comparisons^[66]. Contrary to the trait marker hypothesis, this may suggest that different states of depressive symptoms or choice of different brain regions may affect the results of MRS findings.

The role of glutamate and *N*-methyl-*D*-aspartate receptors has been implicated in the pathophysiology of depression^[67]. In support of that, Auer et al have reported a reduced glutamate level in the anterior cingulate of subjects with major depression^[68].

Vythilingam et al have measured NAA, Cho, Cr, and mI ratios in the brains of unipolar depressed subjects using ^1H -MRSI^[69]. They reported decreased NAA/Cr levels in the right caudate and elevated Cho/Cr level in the right putamen, while there was no global difference of brain metabolites compared to healthy comparison subjects. These findings suggest that depressed subjects would have focal and lateralized, rather than global, abnormality in brain metabolism.

Moore et al reported in a ^{31}P -MRS study that levels of β -NTP in the basal ganglia were 16% lower in

depressed subjects^[70]. Volz et al also reported decreased levels of β -ATP and total ATP values in the frontal lobes of unipolar depression patients^[71].

Based on recent studies, it is conceivable that MRS may help divide major depression into subtypes and treatment-response groups based on neurochemical markers. Sanacora et al have reported that depressed patients designated as melancholic subtype had decreased GABA levels compared to a non-subtype group^[72].

In addition, Renshaw et his group reported that brain purine levels in fluoxetine-responders are lower than those in non-responders^[73].

2) Treatment effect on metabolites in MDD: ECT and SSRIs

Electroconvulsive therapy (ECT) has been reported to induce an increase in Cho resonance^[56] in depressed patients; but the initial increase of Cho resonance following ECT was reversed in a long-term follow-up study^[74]. Occipital GABA concentration has been reported to increase two-fold after ECT^[75], and depressed subjects who were successfully treated with ECT have been reported to have increased NAA and Glx levels in the amygdala^[76]. Also, a decreased Glx level of the anterior cingulate was normalized after ECT in depressed subjects who responded well to treatment^[77].

As mentioned earlier, Sanacora's group demonstrated that occipital GABA concentrations increased after SSRI treatment in depressed patients^[78]. Interestingly, this same group reported slightly decreased occipital GABA levels after cognitive behavioral therapy (CBT), although the result is not statistically significant^[79]. This MRS finding may indicate that CBT has a different treatment effect or site of action than SSRIs or ECT.

3. Bipolar Disorder (BD)

1) General findings

MRS evidence of brain metabolic changes associated with BD is abundant. There have been reports of decreased NAA levels in the frontal cortex, and hippocampus in bipolar subjects, implying decreased neuronal density or neuronal dysfunction^[80-84]. Further, the degree of decrease in NAA levels correlated with duration of illness^[83], according to a report from Deicken et al.

Elevated Glx level in the dorsolateral prefrontal cortex of acute manic patients^[85] have been reported, possibly suggesting a state-dependent chemical shift. But in addition, ^1H -MRS studies have shown that bipolar children and adolescents had higher mI and Glx

concentrations ^[86, 87], calling that suggestion into question.

In this regard, several findings from ³¹P MRS studies are notable. Decreased PME levels were reported for bipolar disorder subjects in euthymic state, with increased levels in depressed/manic state ^[88-90].

More recently, ¹H-MRS studies have demonstrated that there are also alterations in the intensity of the Cho ^[52, 91] and mI resonances ^[92] in bipolar patients.

The possibility of altering brain high-energy phosphate metabolism may have an important implication in optimizing treatment strategies for bipolar disorder. Lyoo et al conducted multinuclear MRS (proton and phosphorous) to explore the change of high-energy phosphate metabolism after oral intake of creatine-monohydrate ^[93]. They reported that the creatine group had increased brain creatine levels and decreased β -NTP levels compared to the placebo group. There have been related reports that oral choline administration increases brain choline level in lithium-treated subjects with bipolar disorder ^[94] and in healthy volunteers ^[94, 95].

Dager et al reported that increased gray matter lactate and Glx levels have been found in medication-free bipolar patients. This finding may be related to a shift to glycolysis in energy metabolism rather than oxidative phosphorylation in BD ^[96].

In a recent review, a hypothesis of mitochondrial dysfunction in bipolar disorder has been suggested based on MRS findings ^[97]. Previous reports of metabolic changes indicative of biochemical pathology in bipolar disorder (generally, reduced NAA, decreased intracellular pH, elevated lactate, increased Glx, increased Cho, and increased mI) can be understood in an integrated way predicated on this hypothesis.

2) Effects of Lithium

Moore and colleagues measured the neurotrophic effects of lithium ^[98] and found a significant increase in NAA levels after treatment in a combined group of bipolar subjects. The same group of researchers ^[99] later reported, using 3-D MRI and brain segmentation, that gray matter volume increased after 4 weeks of lithium treatment. It should be pointed out that Lithium has also been shown in animal studies to convey neurotrophic/neuroprotective effects by increasing levels of a neuroprotective protein ^[100]. These findings taken together support potential neuroprotective effects of lithium treatment.

There is also a report that lithium increases brain PME levels over a two-week period in patients ^[101]. Most recently, the Moore group detected a lithium-induced decrease in total nucleoside triphosphate (NTP) levels on day 7 (11%) and on day 14 (8%) in

eight healthy volunteers who received 900mg/day of lithium. They discussed the findings according to the specific role of the NTPs ^[102].

4. Alzheimer's disease

Alterations in three major metabolites have been detected among patients with Alzheimer's disease (AD) using ¹H MRS studies: NAA, mI, Cho ^[103].

A number of MRS studies have reported decreased NAA concentrations in multiple brain regions in subjects with AD ^[104-108]. Also, there have been reports of increased mI, which is indicative of glial or cell membrane dysfunction, in AD ^[106, 107, 109]. Increased gray matter and decreased in white matter ^[110] Cho levels have been observed in AD ^[107, 111]. The increase in gray matter Cho levels has also been correlated with decreased memory function ^[111] and decreased regional cerebral metabolism ^[112].

Results from ³¹P MRS studies in AD are less consistent. Brown et al reported PME was elevated in the temporoparietal region in Alzheimer's disease ^[113] but other studies failed to show any changes in phosphorous metabolites ^[114, 115].

More recently, Pettegrew showed that PME levels are significantly elevated in mild AD, while they seem to normalize to control levels as AD subjects became moderately demented ^[116]. PDE levels are reported to increase in AD and to be strongly associated with beta-amyloid plaque ^[117, 118].

In a manner analogous to PME, decreased PCr levels have been observed in the prefrontal cortex of mildly demented AD subjects ^[119], while levels normalized with worsening of dementia.

5. Panic Disorder

MRS studies of panic subjects have been pioneered by Dager and his collaborators at the University of Washington, who exploited the fact that the intravenous infusion of 0.5 M/L or 1.0 M/L sodium lactate induces panic attacks in the majority of subjects with panic disorder ^[120, 121]. They observed that only panic responders showed significant differences of lactate/NAA metabolite ratio to lactate infusion compared to comparison subjects ^[121]. Shioiri and colleagues ^[122] reported in a ³¹P-MRS study that there is a significant asymmetry (left > right) of PCr concentration in the frontal lobes in patients with panic disorder, compared to healthy subjects, which suggests abnormalities of phosphorous metabolism in panic subjects. This finding is in line with prior studies using single photon emission computed tomography (SPECT) ^[123] and EEG ^[124], which also noted frontal lobe right-left asymmetries in subjects with panic disorders. Most recently, Massana et al reported

decreased Cr and PCr levels in right medial temporal region in subjects with panic disorder^[125].

Goddard et al measured cortical GABA levels in 14 unmedicated outpatients with panic disorder and 14 age- and sex-matched comparison subjects using ¹H-MRS^[126]. Patients with panic disorder showed a 22% reduction in total occipital cortex GABA concentration (GABA plus homocarnosine). However, the level of decrease in GABA did not correlate with measures of illness or state of anxiety. This study provides preliminary evidence that reduction in GABA levels might contribute to the pathophysiology of panic disorder.

6. Obsessive-Compulsive Disorder (OCD)

Ebert et al measured brain NAA levels using ¹H-MRS in 12 OCD patients and 6 comparison subjects^[127]. Decreased levels of NAA were observed in the right striatum and the anterior cingulate. In another brain ¹H-MRS study of NAA in 13 OCD and healthy comparison subjects^[128], NAA levels were decreased in the left striatum of the patients. These results suggest reduced neuronal density in this region of the brain. In contrast, Ohara et al (1999) did not observe differences in NAA/Cr, Cho/Cr or NAA/Cho ratios in the lenticular nuclei between OCD and normal subjects^[129]. Positron emission tomography (PET) studies have noted that the basal ganglia may play an important role in mediating mechanisms of action for effective treatments in subjects with obsessive-compulsive disorder^[130, 131]. Thus, MRS findings of decreased NAA levels in OCD subjects are in line with a hypothesis that orbitofrontal-subcortical circuit function mediates the symptomatic expression of OCD^[132].

Moore and collaborators conducted a ¹H-MRS study in a 9-year-old boy with OCD and reported a 40% decrease in the caudate Glx resonance after 12 weeks of paroxetine treatment^[133]. The same group later reported, in a study of a 8-year-old girl with OCD, that the post-treatment decrease in Glx resonance was maintained three months after discontinuation of paroxetine^[134]. Rosenberg et al have also reported that caudate composite Glx resonances are greater in treatment-naïve children and adolescents with OCD, compared to healthy comparison subjects, and that the intensity of this resonance decreases significantly with 12 weeks of paroxetine treatment^[135]. In addition, decreases in caudate glutamatergic concentrations correlated with decreases in OCD symptom severity.

More recently, the same group reported, using a validated phantom replacement methodology, increased cytosolic choline, but not NAA or creatine, in the medial thalamus in children with OCD^[136]. These results are consistent with a PET study in adult OCD

subjects which reported a significant decrease in glucose metabolism in orbitofrontal cortex and right caudate with treatment^[137].

7. Post-Traumatic Stress Disorder (PTSD)

In the first MRS study of PTSD, Schuff et al found hippocampal NAA reduction (by 18% and 6% in the right and left hippocampus, respectively), in the absence of hippocampal volume changes relative to healthy comparison subjects^[138]. They later reported hippocampal NAA reduction (by 26%) in combat-related PTSD subjects in the absence of volume changes in the hippocampus and entorhinal cortex^[139]. These findings suggest that hippocampal NAA level changes seem to be more sensitive indicators of PTSD pathology than their volume losses. Recently, Mohanakrishnan et al have also replicated a decrease in hippocampal NAA level, with more prominent changes in the left side, in PTSD subjects^[140].

A decreased NAA level was observed in the basal ganglia in a ¹H-MRS study of acute fire-related PTSD subjects^[141]. Brown et al have also reported that NAA levels of the medial temporal lobe correlated with the level of symptom re-experience in war-related PTSD subjects^[142].

De Bellis et al conducted a ¹H-MRS study to measure anterior cingulate NAA levels in 11 PTSD children and adolescents and 11 comparison subjects^[143], and found levels in the PTSD group were significantly decreased. The same group later reported that NAA levels in anterior cingulate gyrus increased with symptom remission in a boy with PTSD^[144]. These results imply that neuronal pathology in the anterior cingulate may also play a role in mediating symptoms in childhood PTSD.

8. Drug Abuse/ Dependence

Spectroscopy is uniquely well suited to addressing questions within the areas of substance abuse and dependence. In addition to the regrettable fact that distinct neurochemical pathologies follow from self-administering drugs of abuse, one reason is the ability to detect metabolites, or the substances themselves. Ethyl alcohol, for example, can be directly detected with ¹H-MRS, and subjective reports of intoxication have been shown to parallel ¹H-MRS measurement of brain alcohol levels^[145]. There have also been ¹H-MRS studies that indicate alcohol tolerance may be determined by the differences in the interaction of ethanol with brain membranes, possibly reflecting decreased membrane fluidity among alcohol dependent subjects^[146].

According to a study by Parks et al, early relapsers to alcohol use, but not late or non-relapsers, have

decreased cerebellar NAA levels compared to healthy comparison subjects ^[147]. Such effects are apparently reversible, as they also reported that cerebellar NAA levels and volumes increased after 3-month abstinence.

Chronic alcoholism's effects on brain metabolism have been studied using MRS by Schweinsburg and colleagues ^[148], among others. Their findings include lower NAA levels in frontal gray matter in female alcoholics only, while NAA levels in frontal white matter were lower in both male and female alcoholics, suggestive of some gender difference in alcohol effects on brain metabolism.

Regarding other drugs of abuse, similarly decreased NAA levels in the frontal lobes and thalamus of cocaine dependent persons have also been observed. Chang et al reported that cocaine users have decreased NAA in the frontal cortex and increased *myo*-inositol in both frontal gray and white matter ^[149]. Likewise, Li et al reported chronic cocaine abusers had decreased levels of NAA in the left thalamus compared to healthy comparison subjects ^[150].

Following acute administration of cocaine, Christensen and colleagues reported increased levels of Cho and NAA in the basal ganglia, possibly consistent with cellular swelling ^[151] and suggestive of the resultant NAA down regulation following chronic self-administration seen in other studies.

In cocaine-dependent subjects who had not received treatment, Ke et al reported decreased frontal lobe GABA levels ^[152]. Subsequently, prefrontal GABA levels in cocaine subjects, before and after treatment with pramipexole and venlafaxine ^[153], were acquired by Streeter et al. GABA levels in their drug treatment group were increased compared to a placebo group.

In cocaine-dependent polysubstance abusers ^[154], MacKay and colleagues documented altered brain phospholipid metabolites. Among other polysubstance abusers, Christensen et al reported significant decrements in cortical high-energy phosphates (-10% β -NTP and -7% total NTP) ^[155].

More recently, the same group of researchers reported that cerebral PME and PDE levels are increased, and PCr level is decreased, in opiate-dependent polydrug abusers ^[156]. Similar findings come from Silveri and colleagues, who showed evidence of decreased PCr and increased PDE in opiate-dependent subjects during the first month of methadone maintenance therapy, using ³¹P MRS.

Additionally, there have been MRS studies related to the effects of methamphetamine (MA) on the human brain ^[157-161]. It has been reported that abstinent MA users have significantly lower NAA in the anterior cingulate cortex, but not in occipital visual cortex ^[158]. Furthermore, there is some evidence of cumulative

effects in that an inverse correlation of NAA levels with total amount of MA usage has been reported ^[161].

Finally, a recent study by Chang and her colleagues found that subjects with chronic MA dependence, but without comorbid HIV, had significantly decreased NAA levels in the frontal white and gray matter relative to healthy subjects ^[157].

IV. Limitations and pitfalls of clinical MRS.

A major limitation of current clinical MRS is low sensitivity, which in turn leads to poor spatial resolution. High field scanners improve the ability to detect strongly overlapping resonance lines such as glutamate, glutamine, and GABA with ¹H-MRSI and also benefit MRS studies of other nuclei, including ³¹P, ¹³C, and ¹⁹F. Still, patient motion during data acquisition can cause the signal to come from outside the volume of interest (VOI).

In addition, further limitations and exigencies include the fact that the tissue of the VOI is likely to be inhomogeneous, resulting in partial volume effects. Artifacts occurring due to magnetic inhomogeneities result in distortion of the line width of resonance peaks.

Unlike MRI, MRS is dependent on a technique called shimming, entailing the rendering of more homogeneous magnetic fields prior to each acquisition. Larger voxel sizes and longer acquisition times are required, because MRS signals are much weaker than the signals derived with MRI. A final limitation to adumbrate is that nuclei immobile due to binding to macromolecules are invisible to MRS, with a poor signal-to-noise ratio.

A suggestion going forward is that the current state of MRS techniques necessitates substantial work in standardizing measurements between scanning sites to confirm that different MRS findings reflect differences in regional neurochemistry for specific clinical subgroups, rather than different methodologies applied to different populations.

References

1. Mourino, M.R., Radiology, 1991. 180(3): p. 593-612.
2. Kirk, G.S., J.E. Raven, and M. Schofield, Cambridge, 1990.
3. Purcell, E.M., H.C. Torrey, and R.V. Pound, Phys. Rev., 1946. 69: p. 37.
4. Bloch, F., W.W. I-Iansen, and H.E. Packard, Phys. Rev., 1946. 69: p. 127.
5. Chen, W., et al., Magn Reson Med, 1997. 38(4): p. 551-7.
6. Rangó, M., et al., J Cereb Blood Flow Metab, 2001. 21(1): p. 85-91.
7. Moore, C.M. and P.F. Renshaw, *Magnetic resonance spectroscopy studies of affective disorders*, in *Brain imaging in clinical psychiatry*, K.R.R. Krishna and P.M. Doraiswamy, Editors. 1997, Marcel Dekker: New York. p. 185-214.
8. Schmalzing, G., Mol Pharmacol, 1988. 34(6): p. 888-95.
9. Renshaw, P.F., et al., Am J Psychiatry, 1992. 149(11): p. 1592-4.

10. Bolo, N.R., et al., *Neuropsychopharmacology*, 2000. 23(4): p. 428-38.
11. Henry, M.E., et al., *Am J Psychiatry*, 2000. 157(9): p. 1506-8.
12. Strauss, W.L., et al., *Am J Psychiatry*, 1997. 154(4): p. 516-22.
13. Keshavan, M.S., J.A. Stanley, and J.W. Pettegrew, *Biol Psychiatry*, 2000. 48(5): p. 369-80.
14. Stanley, J.A., J.W. Pettegrew, and M.S. Keshavan, *Biol Psychiatry*, 2000. 48(5): p. 357-68.
15. Vance, A.L., et al., *Aust N Z J Psychiatry*, 2000. 34(1): p. 14-25.
16. Delamillieure, P., et al., *Am J Psychiatry*, 2000. 157(4): p. 641-3.
17. Steel, R.M., et al., *Psychiatry Res*, 2001. 106(3): p. 161-70.
18. Yamasue, H., et al., *Neuroreport*, 2002. 13(16): p. 2133-7.
19. Deicken, R.F., et al., *Am J Psychiatry*, 2000. 157(4): p. 644-7.
20. Jakary, A., et al., *Schizophr Res*, 2005. 76(2-3): p. 173-85.
21. Feinberg, I., *J Psychiatr Res*, 1982. 17(4): p. 319-34.
22. Feinberg, I., *Schizophr Bull*, 1990. 16(4): p. 567-70.
23. Pettegrew, J.W., M.S. Keshavan, and N.J. Minshew, *Schizophr Bull*, 1993. 19(1): p. 35-53.
24. Deicken, R.F., et al., *Am J Psychiatry*, 1995. 152(1): p. 126-9.
25. Deicken, R.F., et al., *Psychiatry Res*, 2001. 107(3): p. 125-34.
26. Andreasen, N.C., et al., *Proc Natl Acad Sci U S A*, 1996. 93(18): p. 9985-90.
27. Kegeles, L.S., et al., *Psychiatry Res*, 2000. 98(3): p. 163-75.
28. Ende, G., et al., *Schizophr Res*, 2000. 41(3): p. 389-95.
29. Tebartz van Elst, L., et al., *Biol Psychiatry*, 2005. 58(9): p. 724-30.
30. Gangadhar, B.N., et al., *Am J Psychiatry*, 2004. 161(7): p. 1304-6.
31. Cecil, K.M., et al., *Neuropsychopharmacology*, 1999. 20(2): p. 131-40.
32. Fannon, D., et al., *Biol Psychiatry*, 2003. 54(6): p. 587-98.
33. Gimenez, M., et al., *Neurosci Lett*, 2003. 347(2): p. 97-100.
34. Theberge, J., et al., *Am J Psychiatry*, 2002. 159(11): p. 1944-6.
35. Jayakumar, P.N., et al., *Biol Psychiatry*, 2003. 54(4): p. 491-4.
36. Bustillo, J.R., et al., *Am J Psychiatry*, 2002. 159(1): p. 130-3.
37. Braus, D.F., et al., *Pharmacopsychiatry*, 2001. 34(6): p. 251-3.
38. Braus, D.F., et al., *Eur Neuropsychopharmacol*, 2002. 12(2): p. 145-52.
39. Goff, D.C., et al., *Biol Psychiatry*, 2002. 51(6): p. 493-7.
40. Riehemann, S., et al., *Psychiatry Res*, 2002. 114(2): p. 113-7.
41. Fukuzako, H., et al., *Neuropsychopharmacology*, 1999. 21(4): p. 542-9.
42. Volz, H.P., et al., *Biol Psychiatry*, 1999. 45(9): p. 1221-5.
43. Bustillo, J.R., et al., *Schizophr Res*, 2002. 58(2-3): p. 313-21.
44. Theberge, J., et al., *Am J Psychiatry*, 2003. 160(12): p. 2231-3.
45. Szulc, A., et al., *Pharmacopsychiatry*, 2005. 38(5): p. 214-9.
46. Bertolino, A., et al., *Am J Psychiatry*, 2003. 160(3): p. 483-9.
47. Fukuzako, H., S. Kodama, and T. Fukuzako, *Schizophr Res*, 2002. 58(2-3): p. 201-3.
48. Strauss, W.L. and S.R. Dager, *Biol Psychiatry*, 2001. 49(9): p. 798-802.
49. Bolo, N.R., Y. Hode, and J.P. Macher, *Magma*, 2004. 16(6): p. 268-76.
50. Henry, M.E., et al., *Neuropsychopharmacology*, 2005. 30(8): p. 1576-83.
51. Charles, H.C., et al., *Prog Neuropsychopharmacol Biol Psychiatry*, 1994. 18(7): p. 1121-7.
52. Hamakawa, H., et al., *Eur Arch Psychiatry Clin Neurosci*, 1998. 248(1): p. 53-8.
53. Kumar, A., et al., *Am J Psychiatry*, 2002. 159(4): p. 630-6.
54. Farchione, T.R., G.J. Moore, and D.R. Rosenberg, *Biol Psychiatry*, 2002. 52(2): p. 86-92.
55. Renshaw, P.F., et al., *Biol Psychiatry*, 1997. 41(8): p. 837-43.
56. Ende, G., et al., *Arch Gen Psychiatry*, 2000. 57(10): p. 937-43.
57. Kusumakar, V., et al., *Can J Psychiatry*, 2001. 46(10): p. 959-64.
58. Sonawalla, S.B., et al., *Am J Psychiatry*, 1999. 156(10): p. 1638-40.
59. Exton, J.H., *Biochim Biophys Acta*, 1994. 1212(1): p. 26-42.
60. Duc, C.O. *Recycling the cholines*. in *Int Soc Mag Reson Med VI*. 1997. Vancouver.
61. Khia, A., et al., *NMR Biomed*, 1999. 12(6): p. 357-63.
62. Coupland, N.J., et al., *Biol Psychiatry*, 2005. 57(12): p. 1526-34.
63. Frey, R., et al., *J Psychiatr Res*, 1998. 32(6): p. 411-20.
64. Sanacora, G., et al., *Arch Gen Psychiatry*, 1999. 56(11): p. 1043-7.
65. Petty, F., *J Affect Disord*, 1995. 34(4): p. 275-81.
66. Hasler, G., et al., *Biol Psychiatry*, 2005.
67. Petrie, R.X., I.C. Reid, and C.A. Stewart, *Pharmacol Ther*, 2000. 87(1): p. 11-25.
68. Auer, D.P., et al., *Biol Psychiatry*, 2000. 47(4): p. 305-13.
69. Vythilingam, M., et al., *Biol Psychiatry*, 2003. 54(7): p. 744-50.
70. Moore, C.M., et al., *Am J Psychiatry*, 1997. 154(1): p. 116-8.
71. Volz, H.P., et al., *Eur Arch Psychiatry Clin Neurosci*, 1998. 248(6): p. 289-95.
72. Sanacora, G., et al., *Arch Gen Psychiatry*, 2004. 61(7): p. 705-13.
73. Renshaw, P.F., et al., *Am J Psychiatry*, 2001. 158(12): p. 2048-55.
74. Obergriesser, T., et al., *J Clin Psychiatry*, 2003. 64(7): p. 775-80.
75. Sanacora, G., et al., *Am J Psychiatry*, 2003. 160(3): p. 577-9.
76. Michael, N., et al., *Neuropsychopharmacology*, 2003. 28(4): p. 720-5.
77. Pfeleiderer, B., et al., *Psychiatry Res*, 2003. 122(3): p. 185-92.
78. Sanacora, G., et al., *Am J Psychiatry*, 2002. 159(4): p. 663-5.
79. Sanacora, G., et al., *Biol Psychiatry*, 2005.
80. Cecil, K.M., et al., *Bipolar Disord*, 2002. 4(6): p. 357-65.
81. Winsberg, M.E., et al., *Biol Psychiatry*, 2000. 47(6): p. 475-81.
82. Bertolino, A., et al., *Biol Psychiatry*, 2003. 53(10): p. 906-13.
83. Deicken, R.F., et al., *Am J Psychiatry*, 2003. 160(5): p. 873-82.
84. Chang, K., et al., *Biol Psychiatry*, 2003. 53(11): p. 1059-65.
85. Michael, N., et al., *Psychopharmacology (Berl)*, 2003. 168(3): p. 344-6.
86. Davanzo, P., et al., *Am J Psychiatry*, 2003. 160(8): p. 1442-52.
87. Castillo, M., et al., *AJNR Am J Neuroradiol*, 2000. 21(5): p. 832-8.
88. Kato, T., et al., *J Affect Disord*, 1992. 26(4): p. 223-30.
89. Kato, T., et al., *J Affect Disord*, 1993. 27(1): p. 53-9.
90. Yildiz, A., et al., *Psychiatry Res*, 2001. 106(3): p. 181-91.
91. Moore, C.M., et al., *Bipolar Disord*, 2000. 2(3 Pt 2): p. 207-16.
92. Moore, G.J., et al., *Am J Psychiatry*, 1999. 156(12): p. 1902-8.
93. Lyoo, I.K., et al., *Psychiatry Res*, 2003. 123(2): p. 87-100.
94. Stoll, A.L., et al., *Biol Psychiatry*, 1996. 40(5): p. 382-8.
95. Stoll, A.L., et al., *Biol Psychiatry*, 1995. 37(3): p. 170-4.
96. Dager, S.R., et al., *Arch Gen Psychiatry*, 2004. 61(5): p. 450-8.
97. Stork, C. and P.F. Renshaw, *Mol Psychiatry*, 2005. 10(10): p. 900-19.
98. Moore, G.J., et al., *Biol Psychiatry*, 2000. 48(1): p. 1-8.
99. Moore, G.J., et al., *Lancet*, 2000. 356(9237): p. 1241-2.
100. Chen, R.W. and D.M. Chuang, *J Biol Chem*, 1999. 274(10): p. 6039-42.
101. Yildiz, A., et al., *Biol Psychiatry*, 2001. 50(1): p. 3-7.
102. Yildiz, A., et al., *Psychiatry Res*, 2005. 138(1): p. 51-9.
103. Moore, C.M., B.B. Frederick, and P.F. Renshaw, *J Geriatr Psychiatry Neurol*, 1999. 12(3): p. 107-17.
104. Dixon, R.M., et al., *Brain*, 2002. 125(Pt 10): p. 2332-41.
105. Block, W., et al., *Arch Neurol*, 2002. 59(5): p. 828-34.
106. Huang, W., et al., *Neurology*, 2001. 57(4): p. 626-32.
107. Kantarci, K., et al., *Neurology*, 2000. 55(2): p. 210-7.
108. Doraiswamy, P.M., H.C. Charles, and K.R. Krishnan, *Lancet*, 1998. 352(9141): p. 1678.
109. Ernst, T., et al., *Radiology*, 1997. 203(3): p. 829-36.
110. Tedeschi, G., et al., *Neurology*, 1996. 47(3): p. 696-704.
111. Pfefferbaum, A., et al., *Arch Gen Psychiatry*, 1999. 56(2): p. 185-92.
112. Mielke, R., et al., *Int J Neurosci*, 2001. 107(3-4): p. 233-45.
113. Brown, G.G., et al., *Neurology*, 1989. 39(11): p. 1423-7.
114. Bottomley, P.A., et al., *Radiology*, 1992. 183(3): p. 695-9.
115. Murphy, D.G., et al., *Arch Gen Psychiatry*, 1993. 50(5): p. 341-9.
116. Pettegrew, J.W., et al., *Brain Res Bull*, 2000. 53(4): p. 455-69.
117. Smith, C.D., et al., *Neurobiol Aging*, 1993. 14(1): p. 85-92.
118. Pettegrew, J.W., et al., *Arch Neurol*, 1988. 45(10): p. 1093-6.
119. Pettegrew, J.W., et al., *Neurobiol Aging*, 1994. 15(1): p. 117-32.

120. Dager, S.R., et al., *Am J Psychiatry*, 1994. 151(1): p. 57-63.
121. Dager, S.R., et al., *Arch Gen Psychiatry*, 1999. 56(1): p. 70-7.
122. Shioiri, T., et al., *Biol Psychiatry*, 1996. 40(8): p. 785-93.
123. De Cristofaro, M.T., et al., *Biol Psychiatry*, 1993. 33(7): p. 505-12.
124. Wiedemann, G., et al., *Arch Gen Psychiatry*, 1999. 56(1): p. 78-84.
125. Massana, G., et al., *Neuroimage*, 2002. 16(3 Pt 1): p. 836-42.
126. Goddard, A.W., et al., *Arch Gen Psychiatry*, 2001. 58(6): p. 556-61.
127. Ebert, D., et al., *Psychiatry Res*, 1997. 74(3): p. 173-6.
128. Bartha, R., et al., *Am J Psychiatry*, 1998. 155(11): p. 1584-91.
129. Ohara, K., et al., *Psychiatry Res*, 1999. 92(2-3): p. 83-91.
130. Baxter, L.R., Jr., et al., *Arch Gen Psychiatry*, 1987. 44(3): p. 211-8.
131. Schwartz, J.M., et al., *Arch Gen Psychiatry*, 1996. 53(2): p. 109-13.
132. Saxena, S., et al., *Br J Psychiatry Suppl*, 1998. 35: p. 26-37.
133. Moore, G.J., et al., *J Am Acad Child Adolesc Psychiatry*, 1998. 37(6): p. 663-7.
134. Bolton, J., et al., *J Am Acad Child Adolesc Psychiatry*, 2001. 40(8): p. 903-6.
135. Rosenberg, D.R., et al., *J Am Acad Child Adolesc Psychiatry*, 2000. 39(9): p. 1096-103.
136. Rosenberg, D.R., et al., *J Child Neurol*, 2001. 16(9): p. 636-41.
137. Saxena, S., et al., *Neuropsychopharmacology*, 1999. 21(6): p. 683-93.
138. Schuff, N., et al., *Ann N Y Acad Sci*, 1997. 821: p. 516-20.
139. Schuff, N., et al., *Biol Psychiatry*, 2001. 50(12): p. 952-9.
140. Mohanakrishnan Menon, P., et al., *Psychiatry Res*, 2003. 123(2): p. 101-8.
141. Lim, M.K., et al., *Korean J Radiol*, 2003. 4(2): p. 79-84.
142. Brown, S., et al., *J Neuropsychiatry Clin Neurosci*, 2003. 15(3): p. 367-70.
143. De Bellis, M.D., et al., *Am J Psychiatry*, 2000. 157(7): p. 1175-7.
144. De Bellis, M.D., M.S. Keshavan, and K.A. Harenski, *J Child Adolesc Psychopharmacol*, 2001. 11(3): p. 311-6.
145. Mendelson, J.H., et al., *Alcohol*, 1990. 7(5): p. 443-7.
146. Kaufman, M.J., et al., *Magn Reson Med*, 1996. 35(3): p. 435-40.
147. Parks, M.H., et al., *Alcohol Clin Exp Res*, 2002. 26(9): p. 1368-80.
148. Schweinsburg, B.C., et al., *Am J Psychiatry*, 2003. 160(6): p. 1180-3.
149. Chang, L., et al., *Am J Psychiatry*, 1999. 156(5): p. 716-22.
150. Li, S.J., et al., *Biol Psychiatry*, 1999. 45(11): p. 1481-7.
151. Christensen, J.D., et al., *Biol Psychiatry*, 2000. 48(7): p. 685-92.
152. Ke, Y., et al., *Psychiatry Res*, 2004. 130(3): p. 283-93.
153. Streeter, C.C., et al., *Psychopharmacology (Berl)*, 2005. 182(4): p. 516-26.
154. MacKay, S., et al., *Biol Psychiatry*, 1993. 34(4): p. 261-4.
155. Christensen, J.D., et al., *Magn Reson Med*, 1996. 35(5): p. 658-63.
156. Kaufman, M.J., et al., *Psychiatry Res*, 1999. 90(3): p. 143-52.
157. Chang, L., et al., *Am J Psychiatry*, 2005. 162(2): p. 361-9.
158. Nordahl, T.E., et al., *Psychiatry Res*, 2002. 116(1-2): p. 43-52.
159. Sekine, Y., et al., *Neuropsychopharmacology*, 2002. 27(3): p. 453-61.
160. Smith, L.M., et al., *Neurology*, 2001. 57(2): p. 255-60.
161. Ernst, T., et al., *Neurology*, 2000. 54(6): p. 1344-9.